PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 June 2000 (22.06.00)	
International application No. PCT/CA99/01058	**Applicant's or agent's file reference** DH/12038.20
International filing date (day/month/year) 04 November 1999 (04.11.99)	**Priority date** (day/month/year) 04 November 1998 (04.11.98)
Applicant SEIDAH, Nabil et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

16 May 2000 (16.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. Cupello
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION T.. TY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

DUBUC, Jean, H.
Goudreau Gage Dubuc
The Stock Exchange Tower
Suite 3400
800 Place Victoria
Montreal, Quebec H4Z 1E9
CANADA

Date of mailing (day/month/year)
22 June 2000 (22.06.00)

Applicant's or agent's file reference
DH/12038.20

IMPORTANT NOTIFICATION

International application No.
PCT/CA99/01058

International filing date (day/month/year)
04 November 1999 (04.11.99)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
DUBUC, Jean, H.
Goudreau Gage Dubuc & Martineau Walker
The Stock Exchange Tower
Suite 3400
800 Place Victoria
Montreal, Quebec H4Z 1E9
Canada

State of Nationality:
State of Residence:
Telephone No.: 514 397 4335
Facsimile No.: 514 397 4382
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
DUBUC, Jean, H.
Goudreau Gage Dubuc
The Stock Exchange Tower
Suite 3400
800 Place Victoria
Montreal, Quebec H4Z 1E9
Canada

State of Nationality:
State of Residence:
Telephone No.: 514 397 4335
Facsimile No.: 514 397 4382
Teleprinter No.:

3. Further observations, if necessary:
The new agent's address on the Demand has been considered as a change under Rule 92bis. In case of disagreement, the International Bureau should be notified immediately.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
C. Cupello

Telephone No.: (41-22) 338.83.38

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 9/00

A2

(11) International Publication Number: WO 00/26348

(43) International Publication Date: 11 May 2000 (11.05.00)

(21) International Application Number: PCT/CA99/01058

(22) International Filing Date: 4 November 1999 (04.11.99)

(30) Priority Data:
2,249,648 4 November 1998 (04.11.98) CA

(71) Applicant *(for all designated States except US)*: INSTITUT DE RECHERCHES CLINIQUES DE MONTREAL [CA/CA]; 110, avenue des Pins Ouest, Montreal, Quebec H2W 1R7 (CA).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: SEIDAH, Nabil [CA/CA]; #1412, 200, de Gaspé, Ile-des-Soeurs, Quebec H3E 1E6 (CA). CHRETIEN, Michel [CA/CA]; 195, chemin de la Côte-Ste-Catherine #2208, Outremont, Quebec H2V 2B1 (CA). MARCINKIEWICZ, Mieczyslaw [CA/CA]; 6184, avenue Durocher, Outremont, Quebec H2V 3Y6 (CA). LAAKSONEN, Reijo [FI/CA]; 4566 avenue Hampton, Montreal, Quebec H4A 2L4 (CA). DAVIGNON, Jean [CA/CA]; 768 Hartland Avenue, Outremont, Quebec H2V 2X6 (CA).

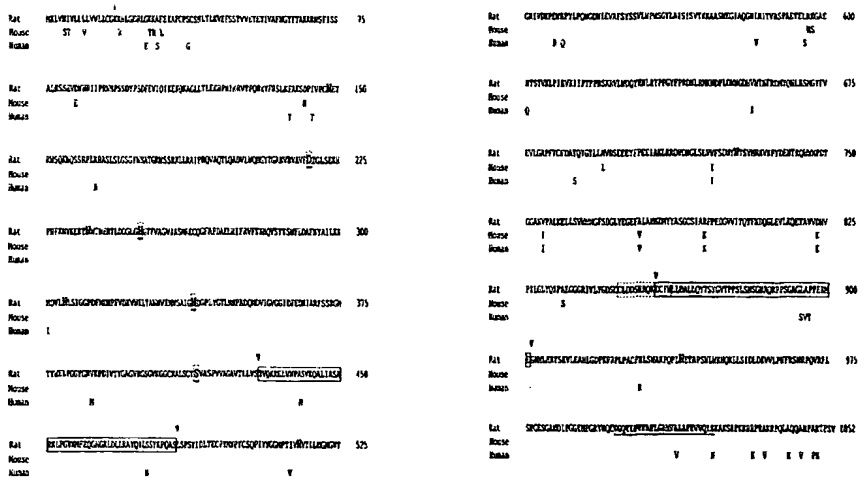
(74) Agents: DUBUC, Jean, H. et al.; Goudreau Gage Dubuc & Martineau Walker, The Stock Exchange Tower, Suite 3400, 800 Place Victoria, Montreal, Quebec H4Z 1E9 (CA).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: MAMMALIAN SUBTILISIN/KEXIN ISOZYME SKI-1: A PROPROTEIN CONVERTASE WITH A UNIQUE CLEAVAGE SPECIFICITY



(57) Abstract

Using RT-PCR and degenerate oligonucleotides derived from the active site residues of subtilisin-kexin-like serine proteinases, we have identified a highly conserved and phylogenetically ancestral human, rat and mouse type-I membrane-bound proteinase called subtilisin-kexin-isozyme-1 (SKI-1). Computer data bank searches reveals that human SKI-1 was previously cloned but with no identified function. A SKI-1 processed fragment is secreted in culture media in a soluble form. *In vitro* studies suggest that SKI-1 is a Ca^{2+}-dependent serine proteinase exhibiting a wide pH optimum for cleavage of proBDNF. Peptides mimicking SKI-1 cleavages sites are also disclosed. SKI-1 prosegment has an *ex vivo* inhibitory effect on SKI-1 activity. The prosegment is also processed and secreted in culture media. One of its fragments is found tightly associated with the SKI-1 soluble form. Therapeutic applications for SKI-1 inhibitors are disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/01058

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N9/64 C07K14/81

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, STRAND, MEDLINE, SCISEARCH, EMBASE, CHEM ABS Data, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X D1	SAKAI JURO ET AL: "Molecular identification of the sterol-regulated luminal protease that cleaves SREBPs and controls lipid composition of animal cells." MOLECULAR CELL, vol. 2, no. 4, October 1998 (1998-10), pages 505-514, XP000867536 ✓ ISSN: 1097-2765 see Results section	7-15, 17-20, 33-40
Y	figures 2,3,5,7	21,22, 33-35
	--- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 August 2000	16. 8 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ALCONADA RODRIG.., A

10

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X D2	DATABASE GENEMBL 'Online! 23 November 1994 (1994-11-23) NOMURA ET AL.: "Human mRNA for KIAA0091 gene, complete cds." XP002136837 ✓ Accession D42053 -& NAGASE ET AL.: "Prediction of the coding sequence of unidentified human genes. III. The coding sequence of 40 new genes (KIAA0081-KIAA0120) deduced by analysis of cDNA clones from human cell line KG-1" DNA RESEARCH, vol. 2, 1995, pages 37-43, XP000874164 tables 1,2	7-15, 37-40

X D3	SIEZEN R J ET AL: "SUBTILASES: THE SUPERFAMILY OF SUBTILISIN-LIKE SERINE PROTEASES" PROTEIN SCIENCE,GB,CAMBRIDGE UNIVERSITY PRESS, CAMBRIDGE, vol. 6, no. 3, March 1997 (1997-03), pages 501-523, XP000856203 ✓ ISSN: 0961-8368 cited in the application	1,7-15, 37-40
Y	figure 2; table 1	2-6,16, 21-23

X D4	EP 0 267 629 A (KYOWA HAKKO KOGYO KK) ✓ 18 May 1988 (1988-05-18)	24,25
Y	see peptide V8-7 page 5, line 24	27-29

Y D5	KONDA YOSHITAKA ET AL: "Proprotein-processing endoprotease furin controls the growth and differentiation of gastric surface mucous cells." JOURNAL OF CLINICAL INVESTIGATION 1997, vol. 99, no. 8, 1997, pages 1842-1851, XP002136832 ✓ ISSN: 0021-9738 figures 11-14 page 1847, right-hand column, last paragraph -page 1849, right-hand column, paragraph 1	21,22, 33-35

	-/--	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y D6	ANDERSON ERIC D ET AL: "Activation of the furin endoprotease is a multiple-step process: Requirements for acidification and internal propeptide cleavage." EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL 1997, vol. 16, no. 7, 1997, pages 1508-1518, XP002136833 ISSN: 0261-4189	2-6,16, 21-23
A	page 1509, right-hand column, last paragraph -page 1510, right-hand column, paragraph 1 figure 6	8-20

Y D7	ZHONG WENYAN ET AL: "Development of an internally quenched fluorescent substrate for Escherichia coli leader peptidase." ANALYTICAL BIOCHEMISTRY, vol. 255, no. 1, 1 January 1998 (1998-01-01), pages 66-73, XP000929725 ISSN: 0003-2697 the whole document	27-29

P,X D8	SEIDAH NABIL G ET AL: "Mammalian subtilisin/kexin isozyme SKI-1: A widely expressed proprotein convertase with a unique cleavage specificity and cellular localization." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA FEB. 16, 1999, vol. 96, no. 4, 16 February 1999 (1999-02-16), pages 1321-1326, XP002136834 ISSN: 0027-8424 the whole document	7-20, 36-40

P,X D9	ESPENSHADE PETER J ET AL: "Autocatalytic processing of Site-1 protease removes propeptide and permits cleavage of sterol regulatory element-binding proteins." JOURNAL OF BIOLOGICAL CHEMISTRY AUG. 6, 1999, vol. 274, no. 32, 6 August 1999 (1999-08-06), pages 22795-22804, XP002136835 ISSN: 0021-9258 the whole document	1-20, 33-40

	-/--	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E D10	WO 00 09677 A (SAKAI JURO ;BROWN MICHAEL S (US); CHENG DONG (US); RAWSON ROBERT B) 24 February 2000 (2000-02-24) claims 1-91 examples 2,3,5,7-9,11 table 4 figures 22,23 ---	1-28, 30-40
T D11	TOURE B B ET AL: "Biosynthesis and enzymatic characterization of human SKI-1/S1P and the processing of its inhibitory prosegment." JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 JAN 28) 275 (4) 2349-58., XP000906874 ---	1-20, 24-40

INTERNATIONAL SEARCH REPORT

[redacted]n patent family members

[redacted]al Application No
PC[redacted]A 99/01058

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0267629 A	18-05-1988	JP 63123397 A	27-05-1988
WO 0009677 A	24-02-2000	AU 5563499 A	06-03-2000

INTERNATIONAL SEARCH REPORT

national application No.
PCT/CA 99/01058

Box I Obs rvations wh re c rtain claims wer found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 41
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

Claim 41 could not be searched because the paramenters X and Y that define the extent of the sequence of SEQ ID NOs: 1,3 or 5 is not defined.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-23, 33-40 (completely)

A soluble protein fragment of a subtilisin-kexin isoenzyme named SKI-1 defined by aminoacids 187 to 996 from the rat (SEQ ID NO:2), mouse (SEQ ID NO:4) or human (SEQ ID NO:6) sequences; a soluble protein fragment from an SKI-1 isoenzyme defined by aminoacids 18 to 137 from SEQ ID NOs: 2, 4 or 6, which is an inhibitor of SKI-1 activity; isolated nucleic acids encoding the protein fragments defined by aminoacids 187 to 996 and 18 to 137 from SEQ ID NOs: 2, 4 and 6; recombinant vectors comprising said nucleic acids including expression vectors containing an inducible promoter; a recombinant host cell comprising the recombinant vector; a method of producing a proteic fragment of SKI-1 enzyme; a method for cleaving an polypeptide which is a proteolytic substrate of SKI-1; a method of inhibiting expression of SKI-1 enzyme by using a ligand which binds to the enzyme or to the nucleic acid; use of SKI-1 polypeptide for treating a disease involving an overexpression of a SKI-1 or a SKI-1 substrate; use of a cell line expressing SKI-1 to screen for inhibitors or enhancers of SKI-1 activity; a method to detect SKI-1 activity in a sample; a diagnostic kit comprising a ligand to SKI-1 polypeptide or nucleic acid; and a composition comprising SKI-1 polypeptide or nucleic acids encoding said polypeptide.

2. Claims: 24-32 (completely)

A peptide of at least 7 amino acids capable of binding and being cleaved by SKI-1; a peptide substrate of SKI-1 which is labelled or fluorogenic, a peptide sustrate of SKI-1 which is labelled by orthoaminobenzoic acid at the N-terminus and by 3-nitrotyrosine at the C-terminus; uses of said peptides to monitor SKI-1 activity, for screening SKI-1 inhibitors and for screening substrates of SKI-1 activity.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 41

Claim 41 could not be searched because the paramenters X and Y that define the extent of the sequence of SEQ ID NOs: 1,3 or 5 is not defined.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
GOUDREAU GAGE DUBUC & MARTINEAU WALKER
Attn. DUBUC, Jean H.
Stock Exchange Tower
800 Place Victoria, Suite 3400
Montreal, Quebec H4Z 1E9
CANADA

Date of mailing *(day/month/year)* 16/08/2000

Applicant's or agent's file reference
DH/12038.20

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/CA 99/01058

International filing date *(day/month/year)* 04/11/1999

Applicant
INSTITUT DE RECHERCHES CLINIQUES DE MONTREAL et al

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2 [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Chantal Meyer

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

WO 00/26348
PCT/CA99/01058

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
DUBUC, Jean, H.
Goudreau Gage Dubuc & Martineau
Walker
The Stock Exchange Tower
Suite 3400
800 Place Victoria
Montreal, Quebec H4Z 1E9
CANADA

Date of mailing (day/month/year)
11 May 2000 (11.05.00)

Applicant's or agent's file reference
DH/12038.20

IMPORTANT NOTICE

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/CA99/01058	04 November 1999 (04.11.99)	04 November 1998 (04.11.98)

Applicant
INSTITUT DE RECHERCHES CLINIQUES DE MONTREAL et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,JP,KP,KR,MA,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   11 May 2000 (11.05.00) under No. WO 00/26348

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
DH/12038.20		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/01058	04/11/1999	04/11/1998
International Patent Classification (IPC) or national classification and IPC C12N9/64		
Applicant INSTITUT DE RECHERCHES CLINIQUES DE MONTREAL et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/05/2000	23.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Paresce, D Telephone No. +49 89 2399 8995

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/01058

I. Basis f the r port

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-79 as originally filed

Claims, No.:

1-41 as originally filed

Drawings, sheets:

1/33-33/33 as originally filed

Sequence listing part of the description, pages:

1-57, filed with the letter of 09.03.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   - ☐ complied with.
   - ☒ not complied with for the following reasons:
     see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   - ☒ all parts.
   - ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21, 24, 27, 35-36
	No:	Claims	22-23, 25-26, 28-34, 37

Inventive step (IS)	Yes:	Claims	1-21, 24, 27, 35-36
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-37
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

This International Preliminary Examination Report is based on amended claims 1-37 submitted by telefax on 26.02.01. The amended set of claims is supported by the original disclosure and therefore complies with the requirements of Article 34(2)(b) PCT.

Re Item IV

Lack of unity of invention

The documents mentioned in this communication are numbered as in the search report, i.e. D1 corresponds to the first document of the search report.

The International Searching Authority (ISA) found that the present application lacks unity of invention as required by Articles 3(4)(iii) and 17(3)(a) PCT (see International Search Report). As all required additional search fees were timely paid by the applicant, the International Search Report covers all searchable claims. The IPEA agrees with the objection put forward by the ISA as to lack of unity (Rule 13.1 PCT). The IPEA found that the present application lacks unity within the meaning of Rule 13.1 PCT. The IPEA was of the opinion that the present set of claims relates to two different inventions (see IPEA/405). The separate inventions/groups of invention are:

1) Claims 1-21, 33-37 are directed to a soluble proteic fragment of a subtilisin-kexin isoenzyme named SKI-1 which has the amino acid sequence defined by amino acids 187-996 from the rat (SEQ ID NO: 2), mouse (SEQ ID NO: 4), or human (SEQ ID NO: 6) SKI-1 sequences. The claims are further directed to a proteic fragment of the SKI-1 enzyme which has the amino acid sequence defined by amino acids 18 to 137 of SEQ ID NOs: 2, 4, or 6 and which is an inhibitor of SKI-1. The claims are further directed to nucleic acid molecules encoding said protein fragments, recombinant vectors comprising said nucleic acid molecules, host cells transformed with said molecule, an expression product produced by said host cells, as well as methods of use of said protein fragments or nucleic acid molecules such as methods for cleaving a polypeptide which is a proteolytic substrate of SKI-1, methods of inhibiting expression of SKI-1, use of SKI-1 for treating disease, use of a cell line expressing SKI-1 to screen for inhibitors or enhancers of SKI-1 activity, diagnostic kits and compositions comprising SKI-1.

2) Claims 22-32 are directed to a peptide of at least 7 amino acids capable of binding and being cleaved by SKI-1, a peptide substrate of SKI-1 which is labelled or fluorogenic, and uses of said peptides to monitor SKI-1 activity.

According to Rule 13.1 PCT, the international application shall relate to one invention or a group of inventions so linked as to form a single general inventive concept. The link between the claims must be a technical relationship which finds expression in the claims themselves and the link must unify the invention to form a single general inventive concept. The IPEA considers that, due to the fact that subtilisin-kexin proteases from human and hamster cells (D1) and substrates for the S1P/SKI-1 enzyme such as SREBP-2 have already been disclosed in the prior art (D1), and due to the essential differences of the identified problems and corresponding proposed solutions, and due to the fact that no other technical features can be distinguished which, in light of the prior art, could be regarded as special technical features, the IPEA considers that there is no single common inventive concept underlying the plurality of claimed inventions of the present application in the sense of Rule 13.1 PCT.

The Applicant was invited to restrict the claims or to pay additional fees (Rule 68.2). As all required additional examination fees were timely paid by the applicant, the International Preliminary Examination Report is based on claims 1-37 of the present application.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The IPEA is of the opinion that claims 22-23, 25-26, 28-34, 37 do not meet the requirements of the PCT with respect to novelty and inventive step for the following reasons:

Polynucleotides with 98% identity to SEQ ID NO: 1, 3, and 5 are known in the prior art. For example, D1 reports the cloning of a hamster and human sterol-regulated luminal protease (site-1 protease, S1P). The hamster S1P shows 98% identity over its entire length with SEQ ID NOs: 2, 4, and 6 of the present

application (see figure 3 of D1). In fact, it is mentioned in the description of the present application that "S1P and SKI-1 appeared to be the same enzyme" (see p. 5). D1 states that, from database searches, S1P was classified as a member of the subtilisin superfamily. The human counterpart of hamster S1P was sequenced previously from a random library of sequences expressed in KG1 cells (see D1, p. 507 and D2). This cDNA sequence was designated KIAA0091. Although D2 does not disclose the function of the KIAA0091 gene product, its potential subtilisin protease function is suggested based on its homology to B. *amyloliquefaciens* subtilisin and based on the existence of a subtilisin active site (see D2).

D1 shows the amino acid sequences of human and hamster S1P in figure 3. A putative signal sequence (the N-terminal 17 amino acids) is shown in figure 1. It is mentioned that, "the initial 17 amino acids are hydrophobic and appear to represent a signal peptide. The hydrophobic sequence terminates at a glycine, which is an ideal substrate for signal peptidase" (p. 507). D1 also mentions that the action of S1P most resembles that of the furins, which are subtilases of the Kex2p-like subfamily that process proteins such as the insulin pro-receptor prior to secretion in animal cells. D1 states that all members of the Kex2p-like family and most other subtilases are synthesized as pre-proteins that must be cleaved proteolytically to be active. Cleavage removes an NH_2-terminal prepro-peptide that inhibits activity (see D1, p. 511). Therefore, D1 suggests the presence of a proteic fragment of the S1P/SKI-1 enzyme which can inhibit S1P activity. Furthermore, D1 describes sterol regulatory element binding proteins (SREBPs) which are substrates of S1P (see abstract D1 and present application p. 6). D1 reports that the Site-1 cleavage reaction requires the participation of a membrane-bound regulatory protein; SCAP. The SCAP/SREBP complex activates S1P, which cuts the SREBPs on the luminal side. The S1P cuts between the leucine and serine of the sequence RSVLS. Recognition requires only the arginine and leucine (see p. 505 and figure 1). D1 describes the development of a fusion protein that contains PLAP in the ER lumen flanked by cleavage sites for signal peptidase and S1P (part of the SREBP-2 sequence) to monitor the activity of S1P (see figure 1 of D1). D1 discloses the expression of S1P in cells transfected with S1P plasmids, and the role of S1P in cholesterol homeostasis and lipid metabolism in animal cells (see discussion).

D3 discloses the identification of hskiaa (GenEMBL accession # D42053 as a human serine protease (see Table 1) and a predicted cleavage site of the presequence at position 18 (see amino acid sequence, figure 2).

D5 describes the role of furin in the growth and differentiation of gastric mucosal cells. A method for suppressing furin expression by its antisense oligonucleotide is disclosed and the effect on cell growth (see abstract, p. 1847-1849).

D6 describes the activation of furin which involves autoproteolytic cleavage. It is mentioned in D6 that the "most thoroughly investigated examples of propeptide-mediated proteinase activation are those of the bacterial serine proteinases, subtilisin and α-lytic protease. The N-terminal propeptides of both enzymes are required for the correct folding of their catalytic domains...the N-terminal propeptides of both bacterial endoproteases are cleaved by an intramolecular reaction...the propeptides remain associated with the catalytic domains through non-covalent interactions and act as potent autoinhibitors." (see p 1508). The bacterial subtilisins are evolutionarily related to the eukaryotic proprotein convertases, such as furin. Activation of furin requires autoproteolytic cleavage of its 83-amino acid propeptide in the RER. Following cleavage in the RER, the furin propeptide remains associated with the enzyme and functions as a potent inhibitor of the endoprotease. Activation of furin, therefore, requires a second cleavage within the autoinhibitory domain at a site containing a P6 arginine (Arg70-Gly-Val-Thr-Lys-Arg75). (see abstract, p. 1509-1510, p. 1512). The relationship of the furin activation pathway to those of other serine endoproteases are discussed (see p. 1514-1515).

In view of the prior art and given the high homology between the amino acid and DNA sequences disclosed in D1, D2 or D3 with those for the SKI-1 enzyme of the present application, the IPEA considers the proteins and DNA sequences described in D1, D2 or D3 to fall under the scope of claim 37 of the present application.

In addition, The IPEA is of the opinion that since "S1P and SKI-1 appear to be the same enzyme" (present application, p.5) all claims that refer solely to "SKI-1", or "an inhibitor of SKI-1 activity", cannot be considered novel. Claims 33-34 do not

contain any **t chnical** features which would make it possible to recognize novelty and inventiveness of the claimed proteins (see paragraph VIII below).

Furthermore, peptide sequences capable of binding to and being cleaved by SIP-1 are disclosed in the prior art (D1). D1 had previously shown that SIP-1 cleaves SREBPs between the leucine and serine of the sequence RSVLS (see p. 505 and figure 1). Therefore, the IPEA is of the opinion that the present claims 22-23, 25-26, 28-32 do not meet the requirements of the PCT with respect to novelty and inventive step.

The subject-matter of claims 1-21, 24, 27, 35-36 has not been made available to the public by any of the available prior art documents and can therefore be regarded as novel. The subject-matter of claims 1-21, 24, 27, 35-36 cannot be derived from the available prior art in an obvious manner and therefore complies with the requirements of Article 33(3) PCT.

VIII. Certain observations on the international application

1) Clarity: Article 6 PCT

Article 6 PCT requires that the claims, which define the matter for which protection is sought (i.e. the object of invention) be clear. This has to be interpreted as meaning not only that a claim from a technical point of view must be comprehensible, but also that it must define clearly the object of the invention, that is to say, it must indicate all the essential features thereof. The essential features are regarded as all features which are necessary to obtain the desired effect, or differently expressed, those features which are necessary to solve the technical problem with which the application is concerned. In other words, all technical features which enable the skilled person to put the claimed matter into practice without undue burden i.e. without experimentation or without application of inventive skill.

The present set of claims are directed to proteic fragments of a known isoenzyme comprising a given sequence, or to "a variant, or enzymatically active part thereof". The term "variant" does not clearly and unambiguously define the scope

of the claim. Without a definition of the length of said DNA and a precise definition of the meant part of the nucleotide sequence in question, this term is absolutely vague and ambiguous. Given the high homology between the amino acid and DNA sequences disclosed in D1, D2 or D3 with those for the SKI-1 enzyme of the present application, the S1P or KIAA0091 or hskiaa proteins are all considered "variants" of SKI-1 that are enzymatically active. The proteins and DNA sequences described in D1, D2 or D3 would, therefore, fall under the scope of these claims.

Claims 2-6, 8-16 refer to a "proteic fragment" of SKI-1. However, the invention of the present application involves the identification of the pro-segment of SKI-1 which acts as an inhibitor of SKI-1 activity. The function of the proteic fragment as an inhibitor of SKI-1 activity is considered to constitute the essential technical feature of the present invention. Thus, in order to comply with the requirements of Article 33(3) as well as Article 6 PCT, it is proposed to introduce the subject-matter of claim 4 into all claims referring to said SKI-1 fragment.

Claim 5 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The subject-matter of this claim is too imprecisely drafted and merely paraphrases the technical problem with which the application is concerned. The claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

Claims 33-34 lack clarity due to the term "SKI-1". The use of an internal arbitrary designation of a protein is meaningless to the person skilled in the art and does not constitute a definition through technical means as required by Article 6 PCT. The protein should be, generally, clearly and unambiguously characterized **in every independent claim** e.g. by reference to technical features, such as sequence information and function, in order to satisfy the requirements of Article 6 PCT as well as Articles 33(2) and (3).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
DH/12038.20		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 99/01058	04/11/1999	04/11/1998
Applicant		
INSTITUT DE RECHERCHES CLINIQUES DE MONTREAL et al		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [X] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

[redacted]nal application No.
PCT/CA 99/01058

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first she t)

Line 6 after "function." delete from "In situ hibridization....." until line 17 "....reminiscent of endosomes."